Am. J. Hum. Genet. 64:963–970, 1999

The Prevalence of Common *BRCA1* and *BRCA2* Mutations among Ashkenazi Jews

Patricia Hartge,[1] Jeffery P. Struewing,[1] Sholom Wacholder,[1] Lawrence C. Brody,[2] and Margaret A. Tucker[1]

[1]Division of Cancer Epidemiology and Statistics, National Cancer Institute, and [2]Genetics and Molecular Biology Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland

Summary

Three founder mutations in the cancer-associated genes *BRCA1* and *BRCA2* occur frequently enough among Ashkenazi Jews to warrant consideration of genetic testing outside the setting of high-risk families with multiple cases of breast or ovarian cancer. We estimated the prevalence of these founder mutations in *BRCA1* and *BRCA2* in the general population of Ashkenazi Jews according to age at testing, personal cancer history, and family cancer history. We compared the results of anonymous genetic testing of blood samples obtained in a survey of >5,000 Jewish participants from the Washington, DC, area with personal and family cancer histories obtained from questionnaires completed by the participants. In all subgroups defined by age and cancer history, fewer mutations were found in this community sample than in clinical series studied to date. For example, 11 (10%) of 109 Jewish women who had been given a diagnosis of breast cancer in their forties carried one of the mutations. The most important predictor of mutation status was a previous diagnosis of breast or ovarian cancer. In men and in women never given a diagnosis of cancer, family history of breast cancer before age 50 years was the strongest predictor. As interest in genetic testing for *BRCA1* and *BRCA2* in the Jewish community broadens, community-based estimates such as these help guide those seeking and those offering such testing. Even with accurate estimates of the likelihood of carrying a mutation and the likelihood of developing cancer if a mutation is detected, the most vexing clinical problems remain.

Received August 28, 1998; accepted for publication January 22, 1999; electronically published March 3, 1999.

Address for correspondence and reprints: Dr. Patricia Hartge, Building EPN, Room 443, NIH, Bethesda, MD 20892-7374. E-mail: hartge@nih.gov

0002-9297/99/6404-0000$02.00

Introduction

In the brief period since *BRCA1* (Miki et al. 1994) and *BRCA2* (Wooster et al. 1995) were sequenced, hundreds of specific mutations in these two large genes have been identified (Breast Cancer Information Core site). Two specific mutations of *BRCA1* (185delAG and 5382insC) and one of *BRCA2* (6174delT) occur relatively frequently among Ashkenazi Jews (Struewing et al. 1995; Oddoux et al. 1996) and substantially increase the likelihood of developing cancers of the breast, ovary, and probably the prostate (Struewing et al. 1997). Even in the absence of established clinical guidelines for people who are found to carry mutations in these genes, the level of risk and the frequency of these specific mutations suggest the possibility of widespread testing in the Jewish population.

Various estimates of the prevalence of mutations in *BRCA1* and *BRCA2* are available from series of patients with breast or ovarian cancers (Modan et al. 1996; Offit et al. 1996; Beller et al. 1997; Levy-Lahad et al. 1997; Fodor et al. 1998) and from registries of families with multiple occurrences of these cancers (Couch et al. 1997; Shattuck-Eidens et al. 1997; Frank et al. 1998). Before predictive models can be extrapolated to community screening, it is important to study larger groups drawn from the general community. We conducted a population survey of 5,318 Jewish men and women in the Washington, DC, area in 1996. By using the survey data, we estimated carriers' risks of developing cancer (Struewing et al. 1997). In the present report, we estimate the effects of personal and family history of cancer on the prevalence of any of the three *BRCA1/BRCA2* mutations common in the Jewish population.

Subjects and Methods

The study design was approved by an institutional review board of the National Institutes of Health. In the spring of 1996, we recruited Jewish men and women in the Washington, DC, area by using posters, advertisements, and radio announcements. Participants enrolled

Table 1

Frequency of Three *BRCA1/BRCA2* Mutations in the Washington Ashkenazi Survey

Characteristic	185 delAG	5382 insC	6174 delT	No. of Mutation Carriers	No. of Subjects	Frequency (%)	95% CI
Sex:							
Male	10	3	18	31	1,576	2.0	1.3–2.7
Female	31	17	41	89	3,742	2.4	1.9–2.9
Cancer in subject:							
Breast	9	6	11	26	288	9.0	5.7–12.3
Ovary	3	0	0	3	17	17.6	0–35.8
Prostate	0	0	2	2	48	4.2	0–9.8
Age (years, in subjects without cancer):							
21–39	10	2	12	24	915	2.6	1.6–3.7
40–59	17	8	29	54	2,684	2.0	1.5–2.5
⩾60	4	4	5	13	1,363	1.0	.4–1.5
Cancer in the family:							
One breast cancer	16	8	19	43	961	4.5	3.1–5.8
Two or more breast cancers	3	4	2	9	87	10.3	3.9–16.7
Ovarian cancer	3	3	5	11	135	8.2	3.5–12.8
Prostate cancer	5	5	7	17	387	4.4	2.3–6.4
Total	41	20	59	120	5,318	2.3	1.9–2.7

at 15 sites during a 9-wk period. After giving written, informed consent, participants completed a brief questionnaire, including information on cancers diagnosed in their first-degree relatives, ages of relatives, and countries of origin. Information on second-degree relatives was collected but is not included in this analysis, except as indicated. Phlebotomists drew a sample of 100–150 μl of blood by using finger-stick procedures and transferred the blood to collection cards. PCR-based assays were used to test DNA samples for the 185delAG and 5382insC mutations in *BRCA1* and the 6174delT mutation in *BRCA2*. A detailed description of the laboratory methods used is available online (Breast Cancer Information Core site). Participants did not receive their individual test results.

We combined carriers of any of the three mutations because the penetrance estimates of the three were not statistically distinguishable in these data, and combining them led to more-stable estimates. Carrier frequencies and approximate 95% confidence intervals (CIs) were calculated for subgroups. Subjects with missing data, such as age at diagnosis of the relative who developed cancer, were excluded from analyses requiring those data. We applied the classification and regression tree (CART) procedure (Breiman et al. 1984) to evaluate potential prediction algorithms without imposing a fixed model of how variables interact and without assuming that the internally generated estimates of cancer risk are correct. Presence of a mutation was the outcome variable, and personal and family history variables were included as potential predictors. The technique recursively partitions the data ("branches") when partitioning on one of the candidate variables significantly reduces the within-set variability. We examined both additive and multiplicative models of subsets of the data, based on the CART models, by fitting linear binomial regression models with the identity link (Wacholder 1986) and logistic regression models. Both linear and logistic regression models fit these data well in the groups with intermediate prevalence rates. The logistic model estimates were substantially higher than the observed frequencies in the groups, with observed prevalence >20%. We therefore present only the linear regression–model estimates and compare them to the observed frequencies.

Results

We recruited 5,318 Jewish men and women from the Washington, DC, area to participate in this research survey. Participants reported an average of 2.7 male and 2.7 female first-degree relatives. Family size was similar in carriers and noncarriers. Among the 3,742 women who volunteered for this study, 288 (8%) reported that they been given a diagnosis of breast cancer. The median age at diagnosis was 50 years, and the median time since the diagnosis was 6 years. Three percent of the men who participated reported a diagnosis of prostate cancer. Overall, 20% of the volunteers reported that at least one of their first-degree female relatives—that is, a mother, daughter, or sister—had been given a diagnosis of breast cancer. Prostate cancer in a father, brother, or son was reported by 7% of volunteers.

In total, 2.3% (95% CI = 1.9–2.7) of the participants carried one of the three founder mutations in *BRCA1* or *BRCA2* (table 1). The frequency was slightly higher in female participants and was twice as high in partic-

ipants aged <40 years as in those aged ⩾60 years. The patterns of volunteering and the underlying likelihood of carrying a mutation combined to determine which subsets yielded the greatest numbers of mutation carriers. Restriction to women would have identified 89 (74%) of the 120 carriers; restriction to participants with breast or ovarian cancer in themselves or their families would have identified 71 (59%).

We analyzed the data as a CART, as shown in table 2. The single most important discriminator was presence of breast or ovarian cancer in the participant. This branching subdivided the 5,290 subjects into one branch with personal history of one or both cancers (9.1% mutation prevalence) and another branch without those cancers (1.9% mutation prevalence). Among the breast or ovarian cancer survivors, age at diagnosis discriminated best. Family history discriminated relatively little if the participant herself had developed cancer, whereas, among the other participants, family history best discriminated carriers from noncarriers. Sex and several other variables were available but did not enter the tree because they did not produce branches with significantly distinct prevalence rates. The lack of branching on a particular variable—for example, the occurrence of ovarian and breast cancer in the same woman versus no such occurrence—can reflect either no difference in mutation prevalence or such small numbers that either the difference cannot be distinguished from chance or the effect of the variable has already been incorporated through another factor.

With data on cancer histories in the respondent and the first-degree relatives only, the lowest prevalence of a final branch on the classification tree was 1.2%, and the highest was 33%. Although many participants expressed difficulty in recalling whether or when a second-degree relative developed breast or ovarian cancer, others were able to report on second-degree relatives. The addition of a variable for breast or ovarian cancers that were reported in second-degree relatives altered only the most detailed level of branching in the lowest prevalence branch. That is, among the 2,870 people with no history of breast or ovarian cancer in themselves or any first-degree relative, the mutation prevalence in those with an affected second-degree relative was 2.3% versus 0.8% in those without.

Acting on the importance of personal history of cancer in classification tree results, we fitted separate linear models for women who had not been given a diagnosis of either breast or ovarian cancer themselves (table 3) and those who had been given a diagnosis of either cancer (table 4). Among women who reported they had not been given a diagnosis of breast or ovarian cancer, the proportion carrying a mutation fell from 3% in those aged <40 years to 1% in those aged ⩾60 years. At each age, a family history of cancer increased the likelihood that women carried a mutation, but none of the observed

Table 2

CART Results: Mutation Frequency in the Washington Ashkenazi Survey

Characteristic	Subjects (*n*)	Frequency (%)
All men and women	5,290	2.3
No breast or ovarian cancer in the subject:	4,993	1.9
No breast or ovarian cancer in family	3,935	1.2
Family history of breast or ovarian cancer:	1,058	4.2
Aged ⩾50 years at study:	567	2.1
One breast cancer in the family	507	1.6
Multiple breast cancers in family	60	6.7
Aged <50 years at study:	491	6.6
No breast, ovarian cancer same woman	470	5.8
Breast and ovarian cancer in same woman	12	33.3
Breast or ovarian cancer in the subject:	297	9.1
Aged ⩾40 years at diagnosis	263	6.8
Aged ⩾60 years at diagnosis	72	1.4
Aged 40–59 years at diagnosis:	191	8.9
No breast or ovarian cancer in family	129	5.4
Breast or ovarian cancer in family	62	16.1
Aged <40 years at diagnosis	34	26.5

NOTE.—Excludes subjects with missing data. Predictors available to model included sex; a history of either breast or ovarian cancer in the participant; a first-degree relative with a history of either breast or ovarian cancer; a history of both a breast cancer and an ovarian cancer occurring in the same woman; a first-degree relative with a history of prostate cancer; a history of prostate cancer in the subject; the decade of age at diagnosis; and the decade of age at participation in this study.

Table 3

Frequency of Carrying Any One of Three Mutations, in Jewish Women Never Given a Diagnosis of Breast or Ovarian Cancer

Age Group and Characteristic	Mutation Carriers/Total	Observed %	Estimated %	95%CI
<40 years	19/690	3	3	2–4
No breast cancer in family	9/566	2	2	1–4
At least one ovarian cancer in family	0/13	0	6	3–14
Breast cancer in family	10/124	8	4	3–6
More than one relative	0/1	0	5	1–21
At least one early diagnosis	5/62	8	5	3–9
40–49 years	23/1,112	2	2	1–3
No breast cancer in family	14/888	2	2	1–3
At least one ovarian cancer in family	3/25	12	6	2–14
Breast cancer in family	9/224	4	4	2–6
More than one relative	0/7	0	5	1–21
At least one early diagnosis	6/81	7	4	2–8
50–59 years	14/811	2	2	1–3
No breast cancer in family	8/636	1	2	.6–2
At least one ovarian cancer in family	0/17	0	6	2–14
Breast cancer in family	6/175	3	3	2–5
More than one relative	2/12	17	5	1–21
At least one early diagnosis	2/56	4	4	2–9
≥60 years	6/806	1	1	.3–2
No breast cancer in family	4/615	1	.5	.2–1
At least one ovarian cancer in family	0/14	0	5	2–14
Breast cancer in family	2/191	1	3	1–5
More than one relative	1/28	4	4	.5–24
At least one early diagnosis	1/67	1	4	2–8

NOTE.—"Family" includes parents, siblings, and children. "Early diagnosis" refers to diagnosis before age 50 years.

or predicted estimates exceeded 20%. For instance, among the 224 women in their forties who reported a positive family history of cancer, only 9 (4%) carried a mutation. In 81 of these women, at least one of the cancers in the family was diagnosed before age 50 years, but only 6 (7%) of the women carried a mutation.

Among women who had been given a diagnosis of breast or ovarian cancer, mutation prevalence fell as age at diagnosis rose (table 4). One-quarter of the 34 women who had been given a diagnosis of cancer before their fortieth birthdays carried a mutation. The estimated prevalence rose to 36% in women with more than one relative with cancer or with an early diagnosis of cancer in the family. Women who had been given a diagnosis of cancer in their forties carried a mutation 10% of the time overall, rising to 15% if another woman in the immediate family had breast or ovarian cancer. Among women who had been given a diagnosis of cancer in their fifties, 7% carried a mutation; after age 60 years, 1% carried a mutation. In total, 25 of the women who developed breast cancer themselves after age 60 years reported breast cancer in the family, but none were mutation carriers.

We compared the prevalence of mutations observed among families with breast cancer identified in this survey to estimates from a logistic regression model based on *BRCA1* mutation analysis in families seen in breast cancer genetics clinics (Couch et al. 1997). As the model predicted, mutation prevalence declined with increasing average age at diagnosis of breast cancer in the family, but the prevalence rates were substantially lower in families from this community sample. For example, for a Jewish family with no ovarian cancer and an average age of <30 years at diagnosis, the projection from the clinic series is 37%; for average age 30–39 years, the projection is 48%. By comparison, we observed 26% prevalence in the families with an average age of <40 years at diagnosis. We also compared our data to a logistic model of *BRCA1* mutation prevalence derived from 798 women in high-risk families drawn from multiple clinics (Shattuck-Eidens et al. 1997) and found fewer than half the predicted *BRCA1* mutation carriers.

One can estimate, on the basis of risks of developing breast cancer seen in the Washington Ashkenazi Study (13% by age 70 years in noncarriers and 56% in carriers), the proportion of breast cancer attributable to mutations. Among 1,000 Jewish women, on average, 20 will carry the mutation, 11 of whom will develop breast cancer—9 more than would if these carriers had no excess risk. On average, 127 of the 980 noncarriers will develop breast cancer. Thus, 11 of the 138 cancers will

Table 4

Frequency of Carrying Any One of Three Mutations, in Jewish Women Given a Diagnosis of Breast Cancer or Ovarian Cancer

Age at Diagnosis, and Characteristic	Mutation Carriers/Total	Observed %	Estimated %	95%CI
<40 years	9/34	26	26	14–44
No breast cancer in family	6/27	22	25	13–43
At least one ovarian cancer in family	0/1	0	28	10–58
Breast cancer in family	3/7	43	31	17–49
More than one relative	0/0	0	36	11–72
At least one early diagnosis	2/4	50	36	18–59
40–49 years	11/109	10	10	6–18
No breast cancer in family	6/77	8	8	4–16
At least one ovarian cancer in family	1/4	25	11	2–50
Breast cancer in family	5/32	16	15	8–25
More than one relative	2/7	29	19	3–64
At least one early diagnosis	3/9	38	19	6–44
50–59 years	6/82	7	7	3–15
No breast cancer in family	2/59	3	5	1–15
At least one ovarian cancer in family	0/3	0	8	.4–62
Breast cancer in family	4/23	17	11	5–22
More than one relative	1/2	50	16	2–66
At least one early diagnosis	2/8	25	16	5–42
⩾60 years	1/72	1	1	.2–9
No breast cancer in family	1/47	2	1	.2–9
At least one ovarian cancer in family	0/0	0	5	.3–1
Breast cancer in family	0/25	0	8	2–22
More than one relative	0/3	0	12	.7–72
At least one early diagnosis	0/10	0	13	3–44

NOTE.—Early diagnosis refers to diagnosis before age 50 years.

test positive for mutation, 9 (6%) of them "due" to *BRCA1* or *BRCA2* mutations.

Discussion

In this large survey of the Jewish community, we observed fewer *BRCA1/BRCA2* mutations in women who reported breast or ovarian cancer in themselves or their families than would be predicted from logistic regression models based on data from cancer genetic screening clinics (Couch et al. 1997; Shattuck-Eidens 1997). The observed prevalence rates were substantially lower than in Israeli ovarian cancer patients (Modan et al. 1996; Levy-Lahad 1997). Our observation of 2% prevalence overall generally accords with other anonymous survey results (Struewing et al. 1995; Oddoux et al. 1996).

In any specific population, the frequency of *BRCA1* or *BRCA2* mutations in subgroups defined by personal and family history of cancer reflects a combination of parameters, beginning with the proportion of the population born with mutations. Differences in subsequent events in both carriers and noncarriers alter the age-specific carrier frequencies, including age-specific cancer risks, any alteration of susceptibility (for example, if oophorectomy and mastectomy were routine in all carriers), survival after cancer diagnosis, and age-specific risks of death from other causes. Furthermore, in particular studies, carrier frequency estimates depend on the numbers of cancers observed, the age distribution of the study group, data accuracy, and selection from the population into the study group. In this population, we estimate that cumulative risks of developing breast cancer by age 50 years were 33% in carriers and 4.5% in noncarriers; risks for ovarian cancer were 7% and 0.4% (Struewing et al. 1997). Cumulative risks at age 70 years were 56% for breast cancer, 13% for ovarian cancer, and 16% for prostate cancer. The noncarriers in this population had estimated risks of 13% for breast cancer, 1.6% for ovarian cancer, and 3.8% for prostate cancer.

Women who have been given a diagnosis of breast cancer represent the group most likely to be offered screening or to request it. They seek genetic information that might bear on their risks of developing contralateral breast cancer or ovarian cancer and the likelihood that their relatives are at risk. Thus, it may be reassuring that only 9% of the study participants who reported having had breast cancer themselves tested positive. However, some of the women who tested negative almost certainly carried other, untested mutations in *BRCA1/BRCA2* or in unidentified cancer genes. Age at diagnosis sharply influenced the likelihood of detecting a mutation, as expected. Indeed, women who developed breast cancer at the oldest ages were not especially likely to carry a mutation. Among women who had already developed

breast or ovarian cancer, the additional information gained from knowing family history was relatively small, because the participant's own cancer history signaled her genotype.

Jewish women given a diagnosis of ovarian cancer also may consider genetic testing. Ovarian cancer occurs less frequently than breast cancer and has a worse survival rate, so this survey included many fewer ovarian than breast cancer survivors. These women were disproportionately likely to carry a mutation (3 [18%] of 17) but not as likely as Israeli ovarian cancer patients have been reported to be (Levy-Lahad et al. 1997). It is not clear why the Israeli patients' frequencies were higher than in the Washington Ashkenazi Survey. Possibly, the populations differed genetically, the fairly small Israeli series included many carriers by chance, or age or some other factor made the Israeli cases disproportionately of genetic origin.

Jewish men given a diagnosis of prostate cancer may consider testing, even though prostate cancer risk is less securely linked to *BRCA1/BRCA2* mutations than are either breast or ovarian cancer. In this population, the kin-cohort analysis showed cumulative risks of prostate cancer at age 70 years similar to those for ovarian cancer (Struewing et al. 1997). Prostate cancer occurs at older ages, and relatively few older men volunteered for this study. Among the 48 prostate cancer survivors, 4% carried a mutation. Similarly, 4% of the 390 participants (mostly women) who reported prostate cancer in the family carried a mutation.

Jewish men and women who have never been given a diagnosis of breast or ovarian cancer constitute another large group potentially interested in genetic testing, depending on their family history. The younger the participants are at screening, the less informative is their own absence of cancer. In this study, 8% of unaffected women aged <40 years carried a mutation if they reported breast or ovarian cancer in the family. By contrast, only 1% of the unaffected women aged ⩾60 years with positive family history were mutation carriers.

Finally, about half of the participants who volunteered for this research study reported no personal history of breast, ovarian, or prostate cancer and no history of these cancers in their immediate families. Such individuals are the least likely to be offered or to request genetic testing, and these data show that such an individual has a relatively small likelihood of being a carrier. However, testing only people with family history will preclude finding many carriers in the general population.

Strengths of the present study include its relatively large size and the inclusion of a broad cross-section of the Jewish community, regardless of cancer history. The low mutation frequencies observed in this community survey presumably reflect the lack of selection factors that increase the proportion of gene-related disease among women enrolled in breast or ovarian cancer screening clinics. Nonetheless, the survey did not constitute a random sample of the entire Jewish community. The study participants were disproportionately female, well-educated, and affiliated with synagogues and other Jewish organizations. As opportunities for cancer gene testing expand, the profile of people deciding whether or not to undergo genetic testing may increasingly resemble this group of volunteers. We have evaluated survival according to carrier status, using an extension of the kin-cohort method, and found no survival advantage or disadvantage (Lee et al. 1999). Thus, the likelihood that a breast cancer survivor carried a mutation was not distorted by differential survival.

Weaknesses of these data include the limitation of genetic testing to the three founder mutations common in individuals of Ashkenazi descent. Further, the findings will not apply to other groups in which specific mutations are more, or less, prevalent. This limitation matters especially if a site-specific mutation is found to be more, or less, penetrant than mutations at other sites on these large genes (Gayther et al. 1997). The lack of accounting for other mutations may not prevent extrapolating to other Jews of Ashkenazi descent, because few other mutations have been reported in the population to date. Other limitations of the data include errors in the reporting of cancers in relatives, but such errors are also likely to occur in the more general setting of counseling and information collection that precedes the decision whether to offer or to accept genetic testing. Furthermore, a registry-based study of an Icelandic founder mutation in *BRCA2* avoided the errors of self-report and found risks no higher than those in the current study (Thorlacius et al. 1998), lending indirect support to the accuracy of the cancer history data in this study. Similarly, an analysis of likely carrier fractions in population-based case-control data produced similar *BRCA1*-related cancer risk estimates (Whittemore et al. 1997)

One potential limitation of the present analysis is its restriction to first-degree relationships. The analytic approach used here offers simplicity but does not exploit all possible information in the family tree. The most complete model needed to predict the likelihood that an individual carries a mutation, described by Berry et al. (1997), combines the dates of birth, death, and diagnosis, if any, of cancers of the breast, ovaries, or prostate in the participant and in each member of the family, accounting for the relation of each to the individual in question. In principle, the model can include cancer history data from the study subject him- or herself, and close or distant relatives. We restricted the present analysis to first-degree relatives because respondents reported difficulty recalling data for more-distant relatives. When restricted to data from first-degree relatives, the full family history model for predicting carrier status

from cancer risk (Berry et al 1997) is the statistical complement of the kin-cohort model for predicting risk from carrier status (Wacholder et al. 1998), the model we developed to estimate breast, ovarian, and prostate cancer risks from this survey. If the cancer risk estimates derived from the current data are correct, then application of the full family history statistical model and the current Ashkenazi risk estimates to additional groups of Ashkenazi individuals ought to predict carrier status with accuracy.

Our study does not address what likelihood of carrying a mutation would make testing appropriate. Research on the information that individuals want and need has been conducted in various settings, leading some observers to recommend individualized approaches to counseling and clinical care (Lerman et al. 1996; Richards et al. 1997). The inherent uncertainty and the possible heterogeneity in cancer risks associated with a mutation complicate the interpretation of any mutations detected. Equally great uncertainty attends the interventions appropriate to reduce cancer risk if an individual is found to carry a mutation. Thus, even if it is possible to develop very accurate models to estimate the likelihood that an individual of Ashkenazi descent carries one of the easily detected founder mutations, the most vexing clinical problems remain.

Acknowledgments

The authors gratefully acknowledge Sonya Baker King for development of laboratory methods and genotyping; Martha Berlin for organizing the survey; Mary McAdams and David Pee for statistical analysis and software development. We thank Rabbi Avis Miller, Pat Barr, Laura Friedan, Deborah Goldstein, Ginny Hartmuller, Dr. Michael Kaback, Rabbi Saul Koss, Dr. Caryn Lerman, Arna Meyer Mickelson, Pat Newman, Dr. Daniella Seminara, Rabbi Matthew Simon, Linda Slan, Joe Waksburg, and Fran Visco for serving on the steering and advisory committees. We are grateful to the volunteers at the data collection centers and to the survey participants.

Electronic-Database Information

URL for data in this article is as follows:

Breast Cancer Information Core site, http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/

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